4. ANTIHYPERTENSIVE AND HYPOTENSIVE DRUGS

A plethora of substances are normally employed to lower the blood pressure, though their effect may be transient. A few of them are used for their hypotensive action. An arbitrary definition of normal adult blood pressure afforded by the **World Health Organization (WHO)-'is a systolic pressure equal to or below 140 mm Hg together with a diastolic pressure equal to or below 90 mm Hg.'**

Antihypertensive drugs are invariably employed in the treatment of hypertension, although a few amongst them, such as : **ganglionic blocking drugs,** do find their scattered applications in a variety of other therapeutic, diagnostic and surgical procedures.

Interestingly, a few of them are used as hypotensive drugs in nonhypertensive subjects. There exist two major categories of '*diastolic hypertension*', namely : (*a*) **primary hypertension** (*e.g.*, essential, idiopathic) ; and (*b*) **secondary hypertension.** However, the *malignant hypertension* is nothing but an acute and rather progressive phase of **primary hypertension.** It has been revealed that there is absolutely no universal therapy for the control and management of primary hypertension ; and, as such, most individual instances do vary widely in response to various therapeutic agents.

In fact, there are several glaring evidences available today that may attribute to certain types of hypertension previously known as **diastolic or essential hypertension,** for instances :

(*a*) Renin-angiotensin pathway,

(*b*) Angiotensin II receptor antagonists and

(*c*) Potential-dependent calcium channels.

4.1. Renin-Angiotensin Pathway

It has already been proved adequately that the prevailing **renin-angiotensin pathway** happens to be an extremely complex, highly regulated pathway which is intimately associated with the ultimate regulation of blood volume, electrolyte balance, and above all the arterial blood pressure. It essentially comprises of *two* cardinal enzymes, known as : *renin* and *angiotensin converting enzyme* (ACE). The most predominant and primary objective of these enzymes are to afford adequate release of angiotensin II from its endogenous precusror, usually termed as **angiotensinogen.** Importantly, angiotensinogen is an **α_2-globulin** having a molecular weight ranging between 58,000 – 61,000. It is essentially made up of 452 amino acids, is available abundantly in the plasma, and is continually replenished by synthesis and secreted by the liver.

In reality, the role of the **renin-angiotensin pathway** in the cardiovascular disorders is extremely vital and critical by virtue of the fact that it exclusively is responsible for the maintenance of blood volume, arterial blood pressure, and the electrolyte balance in the body. Therefore, any slightest abnormalities in this prevailing pathway, such as : excessive release of renin, overproduction of angiotensin II, may ultimately give rise to a plethora of **cardiovascular disorders**.

4.2. Angiotensin II Receptor Antagonists

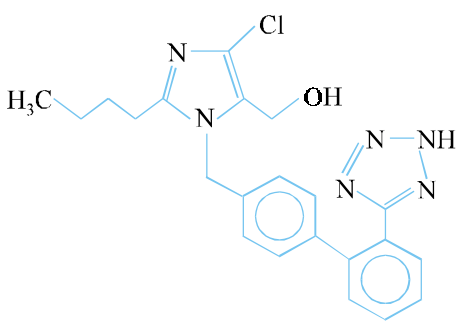
It is, however, pertinent to state here that **angiotensin II receptor** happened to be the first and foremost **'target approach'** towards the historical development of newer drug substances that could possibly inhibit the **renin-angiotensin pathway.** In early 1970s, a tremendous effort was geared into action to develop **angiotensin II receptor antagonists** that was solely based on the *peptide-linked structural analogues* of the **natural agonist.** Efforts in this direction gave birth to several drugs of which a few important ones are given below :

(*a*) **Saralasin**

Sar-Arg-Val-Tyr-Val-His-Pro-Ala

1-(N-Methylglycine)-5-*L*-valine-8-*L*-alanineangeotensin II. It is employed as antihypertensive and as a *diagnostic aid* (*i.e.,* renin-dependent hypertension).

(*b*) **Losartan**



2-Butyl-4-chloro-1-[2′-(1H-tetrazol-5-yl) [1, 1′-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol.

The wonderful drug **'losartan'** was developed in 1982 and since then being used as a potent antihypertensive agent. It specifically blocks the angiotensin II receptor.

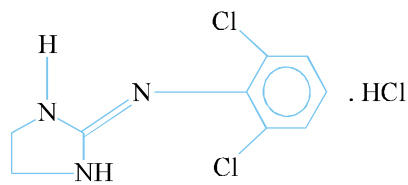
4.3. Potential-Dependent Calcium Channels

It has been well established and demonstrated that the *potential-dependent* Ca^{2+} *channels* are solely critical and important in modulating the influx of Ca^{2+} ; and hence, subsequent inhibition of Ca^{2+} flow through these specific channels results in both vasodilation as well as retarded cellular response to the prevailing contractile stimuli. Based on the proven facts that the *arterial smooth muscle* is found to be more sensitive than the *venous smooth muscle* ; besides, the *coronary and cerebral arterial blood vessels* are observed to be more sensitive in comparison to other *arterial beds**.

Consequent to these pharmacological actions, the calcium channel blockers are found to be profusely beneficial in the treatment of hypertension, and ischemic heart disease (IHD).

Examples. Clonidine hydrochloride, hydralazine hydrochloride, methyl-dopa, diaoxide and sodium nitroprusside.

A. Clonidine INN, Clonidine Hydrochloride BAN, USAN,



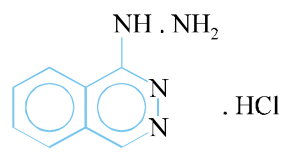
2-(2, 6-Dichloroanilino)-2-imidazoline hydrochloride ; 2-(2, 6-Dichlorophenyl-amino)-2-imidazoline hydrochloride ; 2, 6-Dichloro-N-(imidazolidine-2-ylidene) aniline hydrochloride ; BP ; USP ;

Catapres(R) (Boehringer Ingelheim)

The compound was initially investigated as a nasal vasoconstrictor but incidentally has shown to be an effective drug in the *treatment of mild to severe hypertension and prophylaxis of migraine headache.*

Dose : *0.15 to 0.9 mg daily in 2 or 3 divided doses.*

B. Hydralazine INN, BAN, Hydralazine Hydrochloride USAN,



1-Hydrazinophthalazine monohydrochloride ; Phthalazine, 1-hydrazino-, monohydrochloride ; BP ; USP ; Int. P. ;

Apresoline Hydrochloride(R) (Ciba-Geigy) ;

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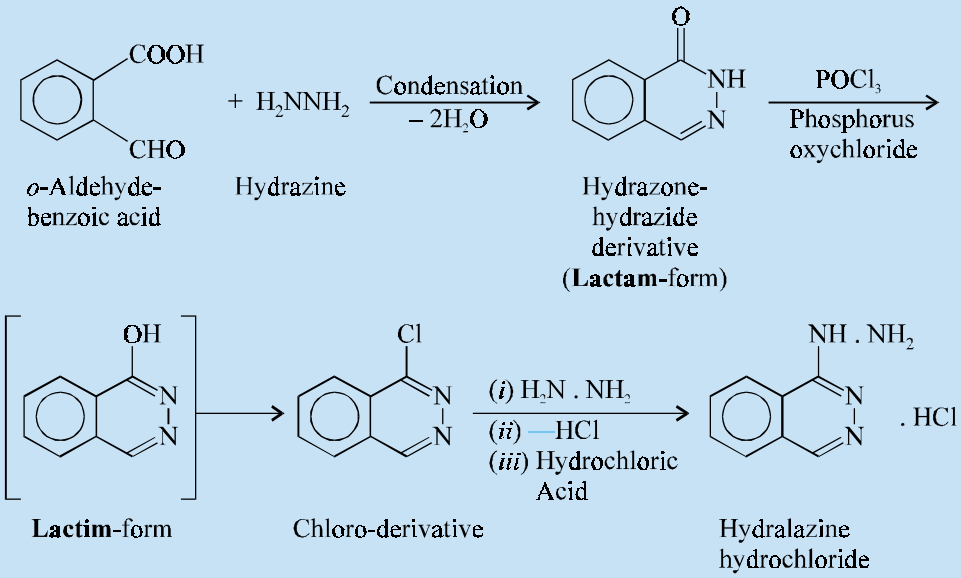
*Swamy VC and Triggle DJ. *Calcium Channel Blockers*, In : Craig GR, Stitzel RE, eds., **Modern Pharmacology with Clinical Applications**, Little Brown, Boston, 5th ed., 1997, 229-34.

Synthesis

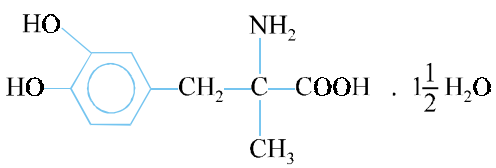


o-Aldehyde benzoic acid, *i.e.*, the half-aldehyde corresponding to phthalic acid, undergoes condensation with hydrazine to yield the **hydrazone hydrazide (lactam-form).** The **lactim-form** of this compound upon chlorination with phosphorus oxychloride gives the corresponding chloro derivative which on *first* treatment with a further mole of hydrazine and *secondly* with a calculated amount of hydrochloric acid affords the official compound.

It is a potent antihypertensive agent which exerts its action mainly by causing direct peripheral vasodilation. It has been observed that its effect on diastolic pressure is more marked and pronounced than on systolic pressure. It is employed in the *treatment of essential and early malignant hypertension usually in conjunction with thiazide diuretics or rauwolfia alkaloids.*

Dose : *Oral, initial, 10 mg 4 times daily for 2 to 4 days, then 25 mg 4 times per day for the rest of the week.*

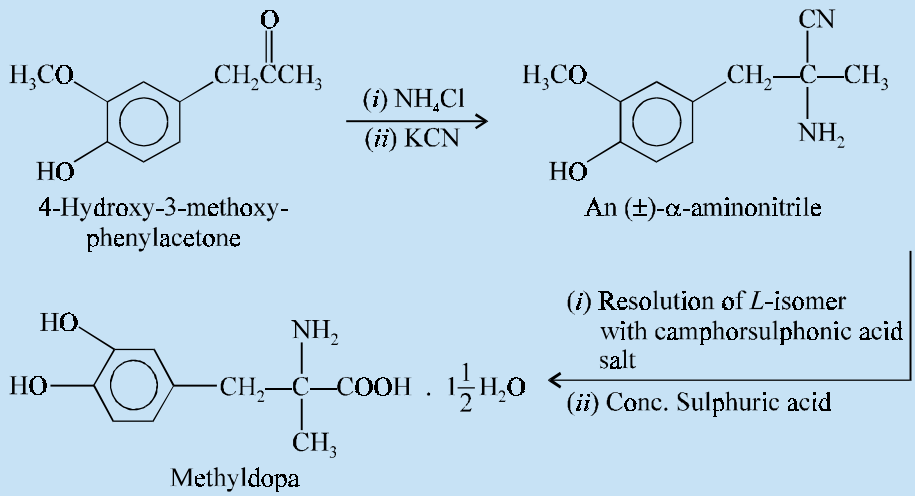
C. Methyldopa INN, BAN, USAN,



L-3-(3, 4-Dihydroxyphenyl)-2-methylalanine sesquihydrate ; L-Tyrosine, 3-hydroxy-α-methyl-, sesquihydrate ; BP ; USP ;

Aldomet$^{(R)}$ (Merck)

Synthesis

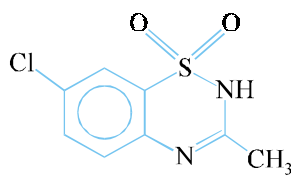


The reaction of 4-hydroxy-3-methoxy phenylacetone with ammonium chloride and potassium cyanide yields the corresponding racemic mixture of α-aminonitrile. The *L*-isomer is separated by means of camphorsulphonic acid salt which on treatment with concentrated sulphuric acid affords two processes simultaneously, namely : hydrolysis of the nitrile function to the acid function ; and cleavage of the methyl ether moiety, to yield the official compound in *its hydrated form.*

Methyldopa is a potent antihypertensive agent that acts centrally by stimulating α-adrenergic receptors. It also helps to minimise the tissue concentrations of adrenaline, noradrenaline and serotonin. It is widely employed *to treat patients having moderate to severe hypertension by reducing the supine blood pressure as well as the standing blood pressure.*

Dose : *Usual, initial dose, oral 250 mg of anhydrous methyldopa 2 or 3 times per day for 2 days ; usual maintenance dosage is 0.5 to 2 g of anhydrous methyldopa everyday.*

D. Diazoxide INN, BAN, USAN,

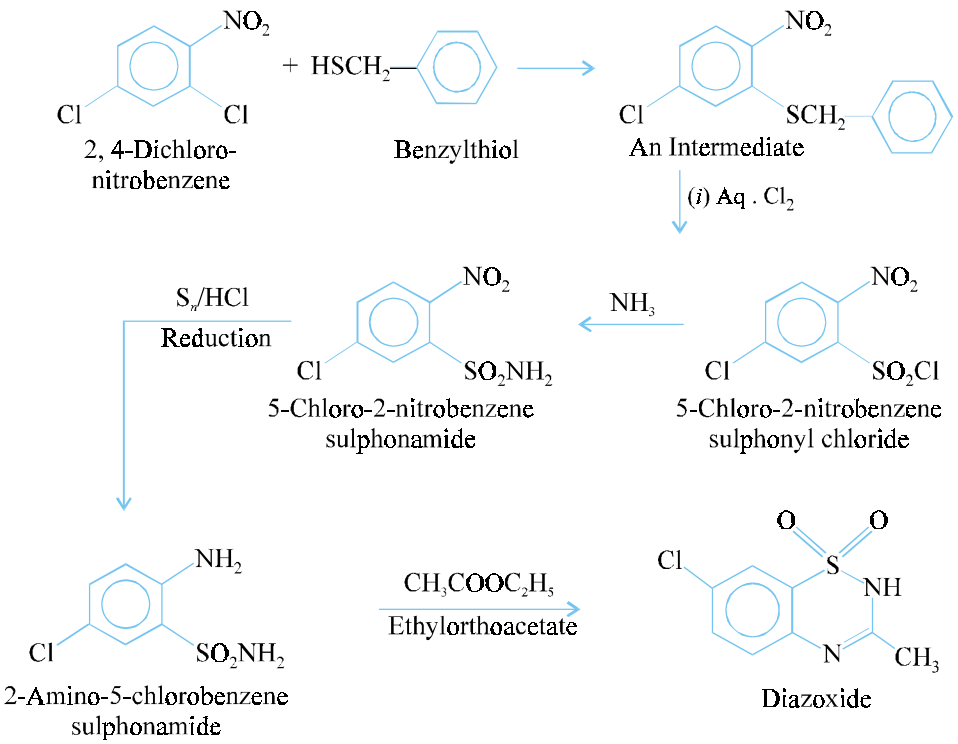


7-Chloro-3-methyl-2H-1, 2, 4-benzothiadiazine 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine, 7-chloro-3-methyl-, 1, 1-dioxide ; BP ; USP ;

Hyperstat(R) (Schering-Plough) ; Eudemine(R) (Allen and Hanburys, U.K.)

Synthesis

Interaction between 2, 4-dichloro-nitrobenzene with benzylthiol affords an intermediate thereby eliminating a mole of hydrogen chloride. The resulting product undergoes debenzylation with concomi-



tant oxidation in the presence of aqueous chlorine gives 5-chloro-2-nitrobenzene sulphonyl chloride which on subsequent treatment with ammonia and reduction yields the corresponding sulphonamide. This on condensation with a mole of ethyl *ortho* acetate yields the official product.

Diazoxide is employed intravenously for the *management and treatment of severe hypertensive crisis thereby lowering the blood pressure by a vasodilator effect on the arterioles.*

Dose : *0.4 to 1 g per day in 2 or 3 divided doses.*

E. Sodium Nitroprusside USAN,

$$Na_2\,[Fe(CN)_5NO]\,.\,2H_2O$$

Sodium nitroferricyanide ; Sodium nitrosylpentacyanoferrate (III) dihydrate ; B.P., U.S.P. ; Nipride(R) (Hoffmann-La Roche) ; Nitropress(R) (Abbott).

Synthesis

$$K_4Fe(CN)_6 \xrightarrow[(ii)\ Na_2CO_3\ (Neutralized)]{(i)\ 50\%\ HNO_3\ (Boiled)} Na_2[Fe(CN)_5NO]\,.\,2H_2O$$

Potassium ferrocyanide — Sodium nitroprusside

Potassium ferrocyanide is first dissolved in 50% HNO_3 and then the solution boiled for 1 hour. The resulting solution is cooled, filtered and neutralized with sodium carbonate, and finally evaporated to crystallization.

It is a short-acting hypotensive agent. It is mostly *employed as a vasodilator in the emergency treatment of hypertensive crises that normally do not respond to other antihypertensive measures.*

Dose : *By continuous infusion of a 0.005 or 0.01% solution in dextrose injection, normally at a rate of 0.5 to 8 mcg per kg body-weight per minute, under physician's observation.*

4.4. Mechanism of Action of Selected Antihypertensive and Hypotensive Drugs

The mechanism of action of certain selected antihypertensive and hypotensive drugs shall be discussed in the section that follows :

4.4.1. Clonidine

The antihypertensive actions are, in part, due to a central action. However, an observed retardation in the sympathetic activity gives rise to a variety of pharmacological actions, such as : vasodilation, bradycardia and occasional atrioventicular block, and a decrease in the release of renin from the kidney ; besides, an enhancement in the vagal activity also affords bradycardia.

Interestingly, the central activity, in part, seem to be the outcome of a specific stimulant action on the **α_2-adrenergic receptors** either located in the vasomotor and cardioinhibitory centres, or in the spinal cord on the preganglionic sympathetic neurons. Besides, it may also exert a peripheral action to reduce the release of norepinephrine from the sympathetic nerves. It has been found to cause stimulation of the **α_2-adrenergic receptors** on the sympathetic nerve terminals, which stimulation ultimately affords a feed back almost negatively to put an end to the release of the ensuing mediator.

4.4.2. Hydralazine

The drug acts on the vascular smooth muscle to afford definite relaxation. Its exact mechanism of action is still not quite vivid and clear. It is found to interfere with Ca^{2+} entry and Ca^{2+} release from the prevailing intracellular reserves ; besides, causing a specific activation of *guanylate cyclase* thereby giving rise to an enhanced levels of cGMP. In fact, the concerted effort of all these biochemical events may afford an apparent vasodilation.

It gets excreted rapidly through the kidneys, and within a span of 24 hours nearly 75% of the total quantum administered appears in the urine as its **'metabolites'** or absolutely unchanged form.

The drug invariably undergoes mainly *three* types of chemical transformations, namely : (*a*) **benzylic oxidation ;** (*b*) **glucuronide formation ;** and (*c*) **N-acetylation by the microsomal enzymes invariably found in the liver and tissues.** It has been observed that **'acetylation'** could pose as a main determinant factor of the rate of hepatic removal of the drug from the blood in circulation ; and, hence, of the prevailing systemic availability of the same.* Consequently, the rapid acetylation aids in an extremely high hepatic extraction ratio ensuing from the circulatory blood, which is virtually responsible for the greater portion of the **first-pass elimination.**

4.4.3. Methyldopa

The drug gets converetd to **α-methylnorepinephrine** that eventually helps in displacing norepinephrine, from the storage sites ; and thus, release as a **'false transmitter'** by means of the prevailing nervous impulses in the adrenergic nerves. Importantly, the **metabolite α-methylnorepinephrine** shows potent **α_2-agonist activity,** and this perhaps acts summararily to lower the blood pressure almost in the same manner as that of clonidine. However, in the spinal cord and the

*Zacest R and Koch-Wesres, *J. Clin. Pharmacol.*, 1972, **13**, 4420.

vasomotor centre, the ultimate results is an observed decrease in the vasomotor outflow, that ultimately is responsible for lowering blood pressure besides decreasing the plasma-renin activity.

4.4.4. Diazoxide

The **drug** at therapeutic dose levels, causes **vasodepression** which is primarily the outcome of arteriolar dilatation, in order that the ensuing orthostatic hypotension is normally minimal. However, certain extent of venous dilatation invariably occurs, which occasionaly is responsible to afford orthostatic hypotension. It has been duly observed that the smooth muscle-relaxing effects are usually caused due to the **hyper-polarization** of vascular smooth muscle by activating ATPase-sensitive K-channels. Hence, it is mostly used in IV as a **'hypotensive drug'** in situations arising from acute hypertensive crises.

Diazoxide is found to be 90% protein-bound ; however, fast and rapid IV administration allows quick-distribution to smooth muscle before it gets bound to protein intimately. Therefore, one may attain a greater and longer-lasting drop in blood pressure through faster rates of IV injection. Interestingly, the '*drug*' is found to persist in blood circulation much longer than the corresponding hypotensive effect. The plasma half-life is 20 to 60 hours in subjects having normal renal function, whereas the corresponding hypotensive effects lasts only 2 to 15 hours.

4.4.5. Sodium Nitroprusside

It happens to release nitric oxide (NO), which is also recognised as endogenous, endothelial-derived relaxing factor. Importantly, 'NO' progressively activated *guanylyl cyclase* strategically located in vascular smooth muscle to effect production of **vasodilatation.** However, its specific actions on the ensuing arterioles minimise the total systemic vascular resistance, and that perhaps is the major cause of the fall in blood pressure it evokes eventually. It has been observed to cause milder action on the *capacitance veins* ; and, therefore, with normal doses, venous return is impaired insignificantly in the *recumbent position.* But in the *upright position* there exists an appreciable *orthostatic hypotension.* Evidently, the observed cardiac output gets enhanced in the recumbent status ; whereas, lowered in the upright status distinctly. Besides, there prevails a variable effect particularly on the *renal plasma flow* and the **glomerular filtration rate,** but it is normally found to be enhanced in the recumbent position. One may also observe the **plasma-renin activity** to get enhanced within a range varying between slight to moderate.